IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	**Jeremy I. Levin, et al.**	
Serial No.:	**unknown**	Group No.: **unknown**
Confirmation No:		Customer No. **25291**
Filed:		Examiner:
For:	**ALKYNYL CONTAINING HYDROXAMIC ACID COMPOUNDS AS MATRIX METALLOPROTEINASE AND TACE INHIBITORS**	

Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Preliminary to the examination of the application, please amend the application as follows:

IN THE SPECIFICATION

Please amend the paragraph beginning on page 1, line 4 to read as follows:

--This is a divisional of copending application(s) serial number 09/492,977 filed on January 27, 2000, which claims the benefit of U.S. Serial No. 60/160,085 filed on January 27, 1999; the entire disclosure of each prior application is hereby incorporated by reference.—

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL909158955US addressed to the Commissioner for Patents, Washington, DC 20231.

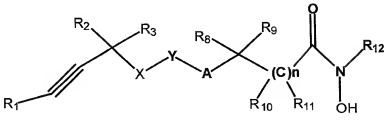
11-13-01
Date

Regina Benson
Regina Benson

IN THE CLAIMS

Please amend claim 1 to read as follows:

1. (Amended) A compound of formula



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

$R_5$is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

$R_7$is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR_5$, COR_5, $-SO_2$-C1-C8 alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, cycloalkyl of 3-6 carbon atoms, -C_4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, S and O, cycloalkyl of 3-6 carbon atoms, -C_5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR_7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y and with the further proviso that Y is not phenyl; and

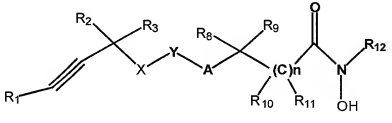
n is 0-2; or a pharmaceutically acceptable salt thereof.

Please amend claim 2 to read as follows:

2. (Amended) A compound according to claim 1 wherein Y is pyridyl, thienyl, furanyl, imidazolyl, triazolyl, or thiadiazolyl.

Please amend claim 5 to read as follows:

5. (Amended) A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula:



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C_5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

$R_5$is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

$R_7$is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR_5$, COR_5, $-SO_2$-C1-C8 alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, cycloalkyl of 3-6 carbon atoms, -C_4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7,

O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, S and O, cycloalkyl of 3-6 carbon atoms, -C_5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR_7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

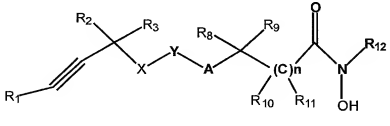
X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y and with the further proviso that Y is not phenyl; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Please amend claim 7 to read as follows:

7. (Amended) A pharmaceutical composition comprising a compound having the formula:



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C_5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

$R_5$is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

$R_7$is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR_5$, COR_5, -SO_2-C1-C8 alkyl, -SO_2-aryl, -SO_2-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, O and S, heteroaralkyl

having from 1-3 heteroatoms selected from N, NR_7, O and S, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, S and O, cycloalkyl of 3-6 carbon atoms, -C5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR_7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that Y is not phenyl; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Please cancel claim 3 and 4 without prejudice.

REMARKS

The present application is a divisional of co-pending U.S. serial no. 09/492,977. The specification has been amended to reflect the complete prosecution history. Applicants have amended the claims to remove subject matter already allowed in the parent application and to correct certain typographical errors.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Applicants believe that the present application is in condition for allowance and respectfully request that the Examiner enter the amendment and allow the application. Favorable treatment of the application is earnestly solicited.

John W. Hogan, Jr.

Reg. No. **32,703**

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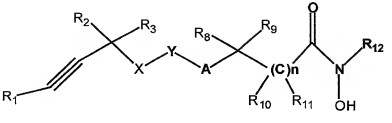
Version with Markings to Show Changes Made

--This is a divisional of copending application(s) serial number 09/492,977 filed on January 27, 2000, which claims the benefit of U.S. Serial No. 60/160,085 filed on January 27, 1999; the entire disclosure of each prior application is hereby incorporated by reference.— ~~This application claims the benefit of U.S. Provisional Application No. 60/160,085, filed January 27, 1999.~~

In the Claims

What is claimed:

1. (Amended) A compound of formula



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, $NR\text{~~7~~}_7$, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

$R\text{~~5~~}_5$ is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

$R\text{~~7~~}_7$ is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR\text{~~5~~}_5$, $COR\text{~~5~~}_5$, $-SO_2$-C1-C8 alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, $NR\text{~~7~~}_7$, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, $NR\text{~~7~~}_7$, O and S, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, $NR\text{~~7~~}_7$, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR~~7~~$_7$, S and O, cycloalkyl of 3-6 carbon atoms, -C$_5$-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

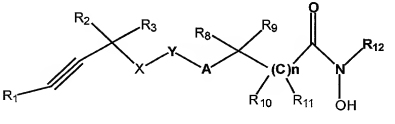
X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y and with the further proviso that Y is not phenyl; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein Y is ~~phenyl,~~ pyridyl, thienyl, furanyl, imidazolyl , triazolyl or thiadiazolyl.

5. (Amended) A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula:



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C$_5$-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR~~7~~$_7$, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

R~~5~~$_5$ is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

R~~7~~$_7$ is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, COOR~~5~~$_5$, COR~~5~~$_5$, -SO_2-C1-C8 alkyl, -SO_2-aryl, -SO_2-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR7, O and S, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, S and O, cycloalkyl of 3-6 carbon atoms, -C5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

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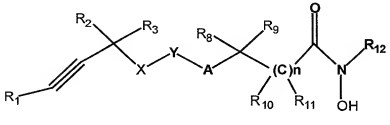

wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

R5 is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

R7 is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, COOR~5~, COR~5~, -SO_2-C1-C8 alkyl, -SO_2-aryl, -SO_2-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR~7~, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR7, O and S, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, S and O, cycloalkyl of 3-6 carbon atoms, -C_5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y and with the further proviso that Y is not phenyl; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Claims 3 and 4 have been cancelled without prejudice.